Combinatorial Synthesis of 2-Thioxo-4-dihydropyrimidinones

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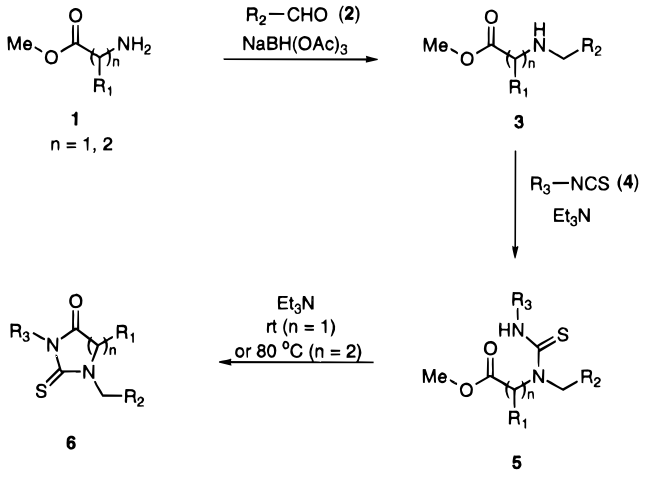
Combinatorial methods of organic synthesis[1] are now established as an important source of compound diversity for drug discovery. These libraries are usually prepared by solid-phase techniques, although solution-phase[2] routes are attracting increasing attention. Recently, we reported[3] the solution-phase synthesis of a thiohydantoin library from α-amino acids, aldehydes, and isothiocyanates. We were also interested in the homologous synthesis of 2-thioxo-4-dihydropyrimidinones[4] (dihydro-2-thiouracils), a class of compounds known[5] to possess biological activity, and disclosed some preliminary results. Here, we present further details of this work and its application to the synthesis of a library comprising 125 discrete compounds.

Results and Discussion

In our thiohydantoin synthesis, the cyclization (Scheme 1, $n = 1$, **5** to **6**) was considerably faster for *N*-alkylamino acid esters compared to their unsubstituted counterparts. Indeed, with secondary amines (**3**), the cyclization occurred during the conditions of isothiocyanate (**4**) addition (rt, 1 mol equiv triethylamine[6]), and we were unable to isolate intermediate **5**. The related six-membered ring (Scheme 1, $n = 2$) cyclization to thioxopyrimidinones was less facile and did not occur likewise. Related cyclizations have been reported[7] using strong acid or base; however, these conditions are less suitable for compounds containing sensitive functionality. We have found that the thioureas undergo the desired cyclization in refluxing triethylamine.[8] Typically, the reaction was complete after 1 day, while further heating (for example, 3 days) did not lead to product decomposition. When the aldehyde component (**2**) was 4-acetoxybenzaldehyde, partial hydrolysis of the acetate ester was observed in the thioxopyrimidinone products.

Scheme 1. Combinatorial Synthesis of Thiohydantoins ($n = 1$) and Thioxopyrimidinones ($n = 2$)



We have investigated a variety of β-amino acid esters, aromatic aldehydes, and isothiocyanates as reaction inputs. Over 80 thioxopyrimidinones were successfully prepared during this validation phase. In general, the thioxopyrimidinone cyclization is more susceptible to steric hindrance than the thiohydantoin synthesis. Thus, thioureas (**7**, Figure 1) derived from cyclohexyl isothiocyanate did not undergo cyclization, whereas thiohydantoins were successfully formed[3] with *tert*-butyl and 1-adamantyl isothiocyanates. In the case of methyl nipecotate, the thiourea intermediate (**8**) also did not cyclize, and decomposed after one week of heating. Finally, anthranilate esters (**9**) gave variable yields in the reductive alkylation and isothiocyanate addition.

We next prepared a library of 125 discrete thioxopyrimidinones from a set of 5 permutations each for the β-amino acid esters, aldehydes, and isothiocyanates (Table 1). Reductive alkylations of the β-amino acid esters were carried out on a large scale, and the crude products divided into portions followed by reaction with individual isothiocyanates. These reactions proceeded uneventfully, except for the reductive alkylation of β-alanine methyl ester (the least hindered β-amino acid), which was plagued by dialkylation. With 3-methoxybenzaldehyde and 4-bromobenzaldehyde, chromatographic purification was necessary to remove the dialkylated product. For benzaldehyde and furfural, only dialkylated products were formed, and the reaction was instead carried out with limiting aldehyde (0.5 mol equiv) to obtain the monoalkylated amino acid after chromatog-

(1) For recent reviews of broad scope, see: (a) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2289. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 555.

(2) We are aware of the following examples published between Jan−Aug 1997: (a) Maehr, H.; Yang, R. *Bioorg. Med. Chem.* **1997**, *5*, 493. (b) Boger, D. L.; Chai, W.; Ozer, R. S.; Andersson, C.-M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 463. (c) Adamczyk, M.; Gebler, J. C.; Grote, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1027. (d) Chng, B. L.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1511. (e) Boger, D. L.; Ozer, R. S.; Andersson, C.-M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1903. (f) An, H.; Cummins, L. L.; Griffey, R. H.; Bharadwaj, R.; Haly, B. D.; Fraser, A. S.; Wilson-Lingardo, L.; Risen, L. M.; Wyatt, J. R.; Cook, P. D. *J. Am. Chem. Soc.* **1997**, *119*, 3696. (g) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (h) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. (i) Pop, I. E.; Déprez, B. P.; Tartar, A. L. *J. Org. Chem.* **1997**, *62*, 2594. (j) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917. (k) Parlow, J. J.; Mischke, D. A.; Woodard, S. S. *J. Org. Chem.* **1997**, *62*, 5908. (l) Baldino, C. M.; Casebier, D. S.; Caserta, J.; Slobodkin, G.; Tu, C.; Coffen, D. L. *Synlett* **1997**, 488. (m) Lawrence, R. M.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553. (n) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 513. (o) Mukhopadhyay, M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083. (p) Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357. (q) Neuville, L.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 4091. (r) Falorni, M.; Giacomelli, G.; Nieddu, F.; Taddei, M. *Tetrahedron Lett.* **1997**, *38*, 4663.

(3) Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230.

(4) For a solid-phase synthesis of dihydropyrimidine-2,4-diones, see: Kolodziej, S. A.; Hamper, B. C. *Tetrahedron Lett.* **1996**, *37*, 5277.

(5) For example, see: Soliman, R. *J. Med. Chem.* **1979**, *22*, 321.

(6) Two other groups have recently independently reported the use of secondary and tertiary amines to effect hydantoin and thiohydantoin cyclization on solid-phase: (a) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603. (b) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090.

(7) (a) Okawara, T.; Nakayama, K.; Furukawa, M. *Chem. Pharm. Bull.* **1983**, *31*, 507. (b) Lorente, A.; Aurrecoechea, L. M. *Heterocycles* **1994**, *38*, 1077.

(8) These conditions were used to cyclize ureas derived from penicillamine: Hatam, M.; Köpper, S.; Martens, J. *Heterocycles* **1996**, *43*, 1653.

S0022-3263(97)01302-9 CCC: $14.00

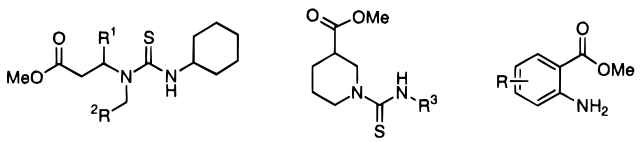


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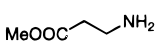
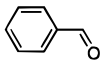
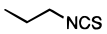
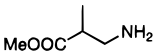
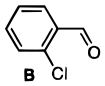
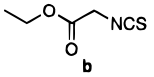
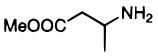
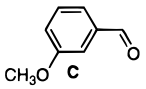
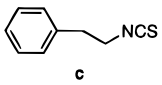
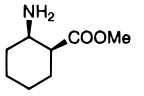
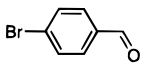
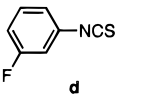
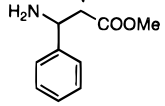
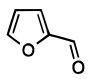
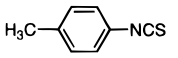
Figure 1.

Table 1. Building Blocks for the Thioxopyrimidinone Library

β-Amino Acid Esters	Aldehydes	Isothiocyanates
 1	 A	 a
 2	 B	 b
 3	 C	 c
 4	 D	 d
 5	 E	 e

raphy. With the more hindered 2-chlorobenzaldehyde, no dialkylation was observed, and the crude product was used directly.

In some cases, the thiourea intermediates (**5**) in our library underwent cyclization to the thioxopyrimidinone without the need for heating. This was particularly so for compounds containing ethyl isothiocyanatoacetate as a building block. In our earlier thiohydantoin synthesis, the final purification consisted of an aqueous wash with glycine as a scavenger. We have since found that aminomethylated polystyrene[9] is a convenient means of removing excess aldehyde and isothiocyanate. This avoids the need for an aqueous workup[10] and was the protocol used for the thioxopyrimidinone library. The purity of the compounds was assessed by ^{1}H NMR, MS, and HPLC analysis (for 25 representative examples, see Table 2). Five of these compounds (**10**−**14**, Figure 2) were chromatographed and characterized fully (see Experimental Section).

In summary, we have demonstrated the utility of the three-step sequence (reductive alkylation, isothiocyanate addition, cyclization) for the combinatorial synthesis of thioxopyrimidinones. Two of the three building blocks, aldehydes and isothiocyanates, are readily available with high diversity. Commercially available β-amino acids are less abundant, but they can be prepared[11] by homologation of the α-amino acid.

Table 2. Mass Recovery and HPLC Purity of Representative Thioxoprimidinones

thioxoprimidinone	mass recovery[a] (%)	HPLC purity (%)	thioxoprimidinone	mass recovery[a] (%)	HPLC purity (%)
1Ae	86	75	**3De**	70	70
1Bc	87	85	**3Eb**	63	60
1Cd	84	73	**4Ae**	96	83
1Db	79	87	**4Bd**	115	91
1Ec	101	81	**4Cb**	116	80
2Aa	71	61	**4Dd**	116	91
2Bd	92	84	**4Eb**	112	70
2Cc	62	78	**5Ac**	95	87
2De	99	81	**5Ad**	108	85
2Eb	64	60	**5Cd**	92	83
3Ac	67	80	**5Db**	101	85
3Ba	66	79	**5Ea**	89	72
3Cd	63	59			

[a] Calculated as the ratio of isolated mass over theoretical yield, expressed as a percentage.

Experimental Section

General. For general methods and instrumentation, see ref 3. IR, ^{1}H, and ^{13}C NMR spectra were recorded in $CDCl_3$; ^{1}H and ^{13}C NMR were taken at 300 and 75 MHz, respectively. Methyl esters **2**−**5** (Table 1) were prepared from the corresponding β-amino acids by reaction with $SOCl_2$ and MeOH, followed by recrystallization from EtOH and Et_2O. Methyl β-aminobutyrate (**3**, Table 1) was obtained as a yellowish syrup which was insoluble in CH_2Cl_2. Reductive alkylations with this compound were carried out in MeOH.

Library Synthesis. A solution of β-amino acid methyl ester hydrochloride salt (0.5 mmol), triethylamine (1.1 mol equiv), aldehyde (1.1 mol equiv), and sodium triacetoxyborohydride (1.5 mol equiv) in CH_2Cl_2 was stirred overnight at rt and then quenched with water. The organic phase was washed with water (2×) and dried over $MgSO_4$, and aliquots were evenly distributed into 1.5 mL vials. Triethylamine (14 μL, 0.1 mmol) and isothiocyanate (0.11 mmol) were added into each vial, and the solution shaken for 3 h. Aminomethylated polystyrene resin[12] (0.2−0.5 mol equiv) was added, and the vials were shaken overnight. The resin was filtered off, and the solution was heated at 80 °C for 1 day. The remaining solvent and triethylamine were finally removed by evaporation in a SpeedVac to yield the crude thioxopyrimidinones. Compounds **10**−**14** were chromatographed on silica (hexanes−ethyl acetate 75:25 eluent).

1-(Phenylmethyl)-3-(2-phenylethyl)-tetrahydro-2-thioxo-4(3*H*)-pyrimidinone (**10**, thioxopyrimidinone **1Ac**): 22 mg, 67%; pale yellow foam; IR ν_{max} 1705 cm^{-1}; ^{1}H NMR δ 2.61 (2H, t, J = 6.8 Hz), 3.01−3.06 (2H, m), 3.37 (2H, t, J = 6.8 Hz), 4.54−4.59 (2H, m), 5.29 (2H, s), 7.20−7.38 (10H, m); ^{13}C NMR δ 31.4, 33.9, 43.3, 47.7, 58.2, 126.3, 127.8, 128.1, 128.3, 128.9, 129.1, 135.4, 138.7, 165.8, 181.7. HRMS calcd for $C_{19}H_{20}N_2OS$ 324.12964 (M^+), found 324.12929. HPLC purity 91%.

1-[(4-Bromophenyl)methyl]-3-(4-methylphenyl)-5-methyl-tetrahydro-2-thioxo-4(3*H*)-pyrimidinone (**11**, thioxopyrimidinone **2De**): 38 mg, 94%; white solid, mp 144−146 °C; IR ν_{max} 1719 cm^{-1}; ^{1}H NMR δ 1.22 (3H, d, J = 7.1 Hz), 2.40 (3H, s), 2.82−2.90 (1H, m), 3.40 (1H, dd, J = 10.9, 13.2 Hz), 3.60 (1H, dd, J = 5.8, 13.2 Hz), 5.23 (1H, d, J = 14.8 Hz), 5.34 (1H, d, J = 14.9 Hz), 7.02−7.53 (8H, m); ^{13}C NMR δ 12.8, 21.3, 35.6, 50.0, 57.5, 122.2, 128.8, 129.7, 129.8, 132.0, 134.4, 137.4, 138.2, 169.4, 182.4. HRMS calcd for $C_{19}H_{19}BrN_2OS$ 402.04016 (M^+), found 402.03894. HPLC purity 86%.

1-[(2-Chlorophenyl)methyl]-3-propyl-6-methyl-tetrahydro-2-thioxo-4(3*H*)-pyrimidinone (**12**, thioxopyrimidinone **3Ba**): 19 mg, 60%; pale yellow foam; IR ν_{max} 1703 cm^{-1}; ^{1}H NMR δ 0.95 (3H, t, J = 7.4 Hz), 1.24 (3H, d, J = 6.7 Hz), 1.64−1.78 (2H, m), 2.56 (1H, dd, J = 1.9, 16.2 Hz), 2.84 (1H, dd, J = 6.3, 16.2 Hz), 3.70 (1H, dp, J = 1.8, 6.7 Hz), 4.23 (1H, ddd, J = 6.3,

(9) For the first report of polymer-bound reagents as scavengers in solution-phase library synthesis, see: Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193.

(10) We also tried using the resin to effect thioxopyrimidinone cyclization as well as scavenging excess reagents. However, the results were less satisfactory than with triethylamine. It is possible that stronger polymer-bound bases would accomplish this transformation.

(11) For example: (a) Pelleti, J.; Seebach, D. *Liebig's Ann.* **1995**, 1217. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; VCH: Weinheim, 1997.

(12) From Nova Biochem, loading 1.62 mmol/g.

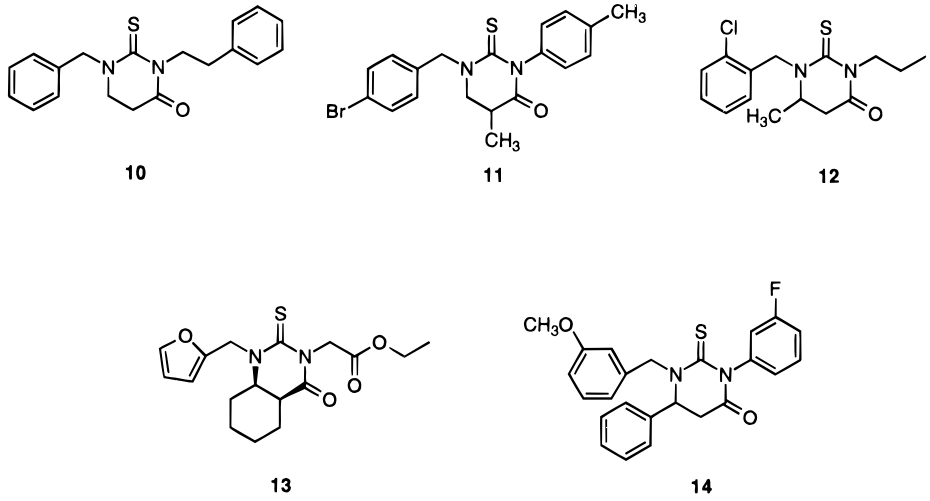


Figure 2.

9.4, 12.8 Hz), 4.43 (1H, ddd, J = 6.0, 9.3, 13.1 Hz), 4.80 (1H, d, J = 15.8 Hz), 6.02 (1H, d, J = 15.8 Hz), 7.24−7.42 (4H, m); ^{13}C NMR δ 11.2, 16.8, 21.2, 37.8, 48.0, 49.9, 54.1, 127.3, 128.8, 129.2, 129.8, 133.3, 133.4, 165.2, 180.9. HRMS calcd for $C_{15}H_{19}N_2OS$ 275.12180 ([M − Cl]$^+$), found 275.12195. HPLC purity 82%.

1-(2-Furylmethyl)-3-(carbethoxymethyl)-*cis*-octahydro-2-thioxo-4(*3H*)-quinazolinone (**13**, thioxopyrimidinone **4Eb**): 28 mg, 80%; pale yellow syrup, IR ν_{max} 1709, 1743 cm^{-1}; ^{1}H NMR δ 1.28 (3H, t, J = 7.0 Hz), 1.22−1.82 (7H, m), 2.48 (1H, br d, J = 13.2 Hz), 2.92 (1H, br s), 3.64−3.71 (1H, m), 4.21 (2H, q, J = 7.2 Hz), 4.74 (1H, d, J = 15.3 Hz), 4.98 (1H, d, J = 16.9 Hz), 5.35 (1H, d, J = 17.0 Hz), 5.69 (1H, d, J = 15.4 Hz), 6.37 (1H, t, J = 1.7, 3.4 Hz), 6.44 (1H, d, J = 2.9 Hz), 7.39 (1H, d, J = 2.4 Hz); ^{13}C NMR δ 14.1, 21.0, 24.4, 24.7, 25.8, 40.2, 47.4, 50.0, 57.4, 61.3, 109.8, 110.7, 142.6, 149.1, 167.8, 168.7, 179.4. HRMS calcd for $C_{17}H_{22}N_2O_4S$ 350.13004 (M$^+$), found 350.12851. HPLC purity 82%.

1-[(3-Methoxyphenyl)methyl]-3-(3-fluorophenyl)-6-phenyl-tetrahydro-2-thioxo-4(3*H*)-pyrimidinone (**14**, thioxopyrimidinone **5Cd**): 29 mg, 68%; pale yellow foam, mp 54−60 °C; IR ν_{max} 1715 cm^{-1}; ^{1}H NMR δ 3.08 (1H, dd, J = 1.8, 16.4 Hz), 3.25 (1H, dd, J = 6.8, 16.4 Hz), 3.81 (3H, s), 4.16 (1H, d, J = 15.0 Hz), 4.94 (1H, d, J = 6.4 Hz), 6.48 (1H, d, J = 15.0 Hz), 6.88−7.49 (13H, m); ^{13}C NMR δ 39.1, 55.3, 56.7, 57.0, 113.4, 113.9, 115.5, 115.7, 120.2, 125.5, 128.9, 129.6, 130.0, 130.2, 136.1, 137.1, 140.6, 140.8, 160.1, 164.5, 182.0. HRMS calcd for $C_{24}H_{21}N_2O_2SF$ 420.13077 (M$^+$), found 420.12820. HPLC purity 91%.

Acknowledgment. This work was supported by grants from the National Science and Technology Board of Singapore.

Supporting Information Available: ^{1}H NMR spectra for thioxopyrimidinones **10**−**14** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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